HIV-1 INTEGRATION SITE DETERMINES THE TRANSCRIPTION FATE AND PERSISTENCE OF INTEGRATED PROVIRUSES

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BACKGROUND

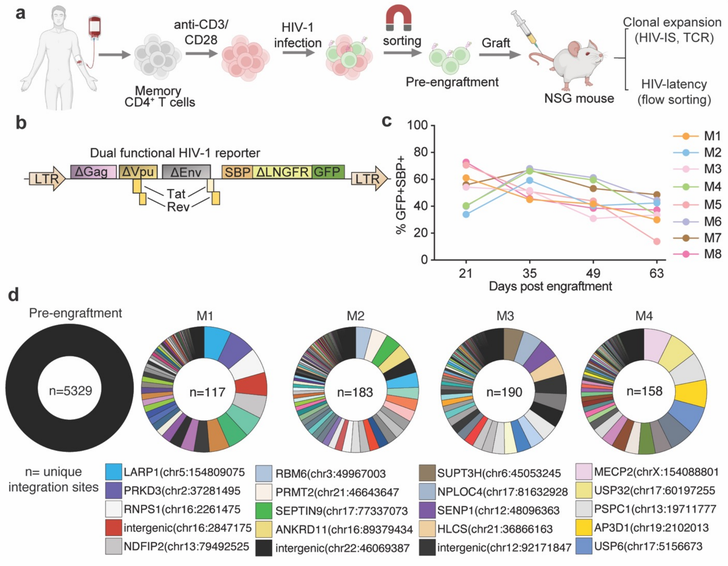
- The latent reservoir of HIV-1 is the major barrier to achieving a cure.
- The rarity of cells that constitute the latent reservoir poses a challenge to investigating the mechanisms of persistence, including clonal expansion and immune evasion.
- The site of HIV-1 integration into host DNA can influence proviral latency and drive clonal expansion via insertional mutagenesis.
- Current models (*in vitro/in vivo*) do not allow the evaluation of the relative contribution of the proviral integration site on latency and expansion in a clone-specific manner.
- The HIV-1 latency mouse (HIVLM) model described in this study allows to investigate the impact of proviral integration sites on clonal expansion and latency in the absence of immunological or viral cytocidal selection pressure imposed on infected cells.

METHODS

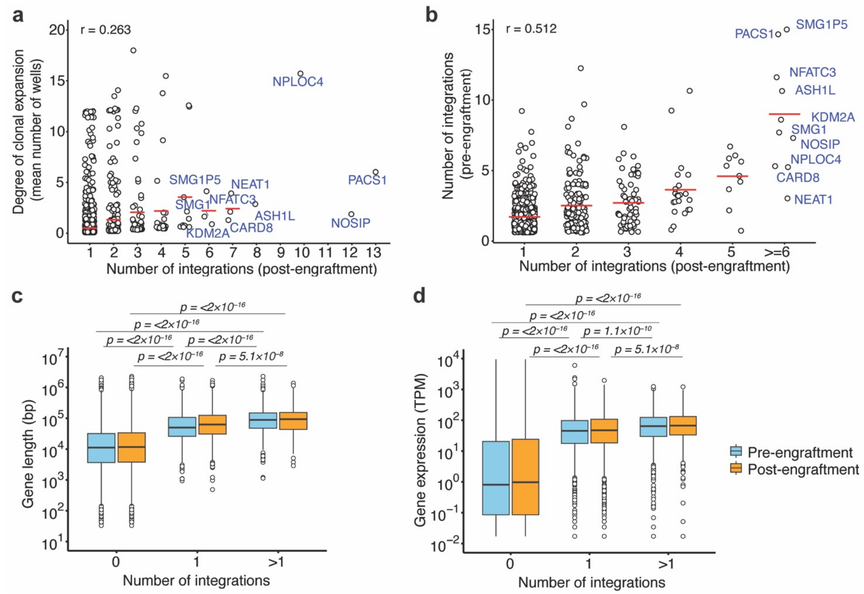
- Human memory CD4⁺ T cells infection with dual-functional, replication-incompetent HIV-1 reporter virus (V1/SBP-GFP) and sorting of infected cells.
- Engraftment of reporter HIV-1-infected primary memory CD4⁺ T cells into immunocompromised NSG mice.
- Flow-cytometry-based analysis of HIV-1 infected human cells post-engraftment in mouse peripheral blood and tissues.
- HIV-1 integration site sequencing and clonal expansion estimation using PRISM-seq.

RESULTS

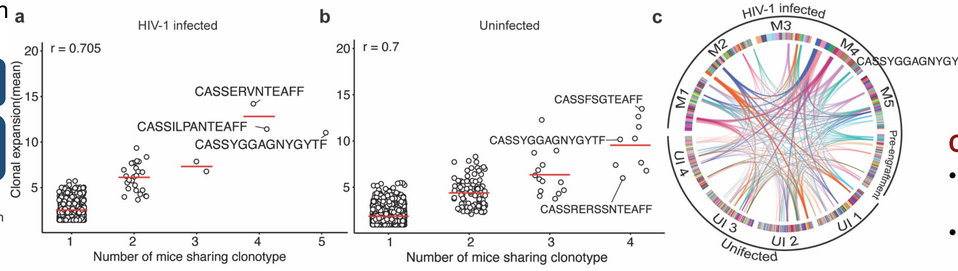
Long-term survival and clonal expansion of HIV-1 infected memory CD4⁺ T cells *in vivo* in the HIVLM model



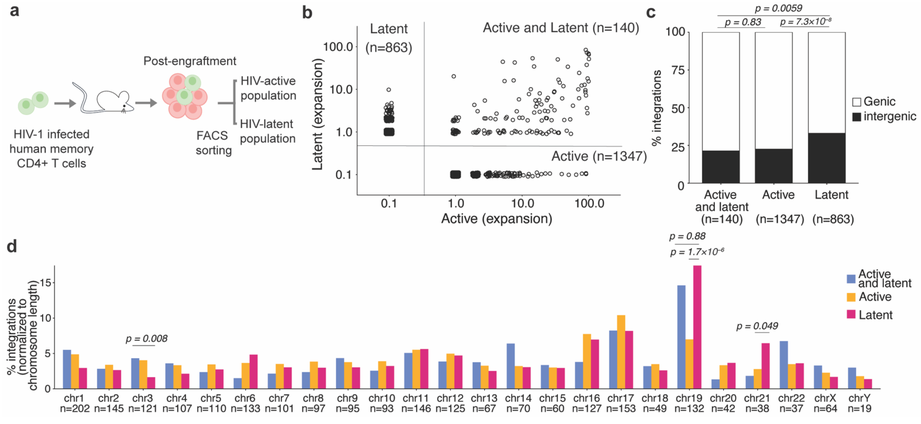
HIV-1 integration into specific genes does not predict clonal expansion



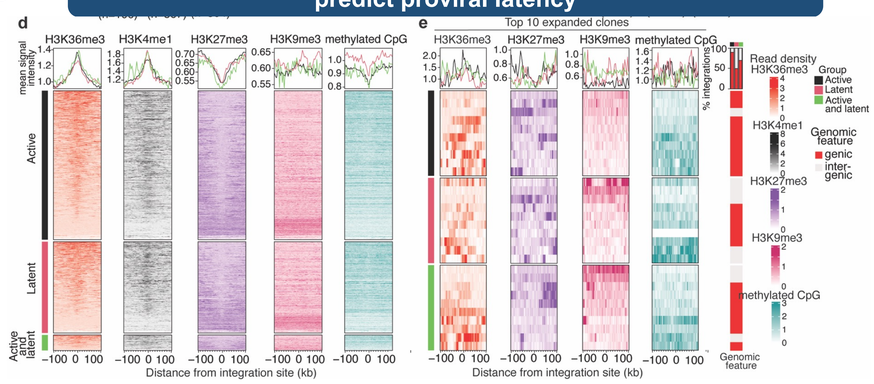
TCR identity dictates the extent of clonal expansion



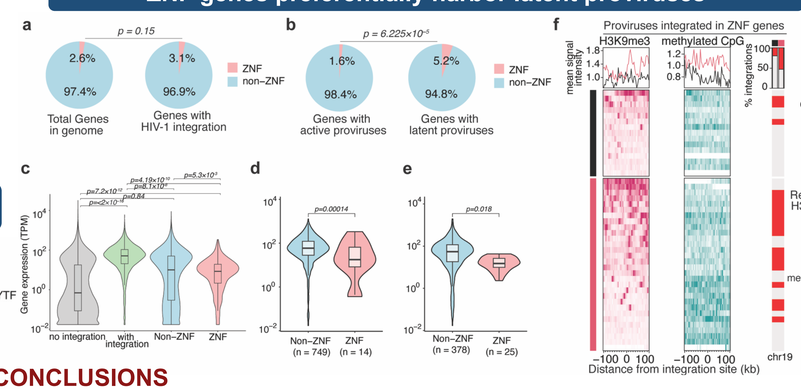
Differential host genomic location of active and latent proviruses



Genomic and epigenetic features at the HIV-1 integration site predict proviral latency



ZNF genes preferentially harbor latent proviruses



CONCLUSIONS

- Proviral integration into specific genes does not drive clonal expansion of infected memory CD4⁺ T cells months after engraftment in the HIVLM model.
- T cell receptor identity better predicts the extent of expansion of infected cell clones, suggesting HIV-1 acts as a passenger during cell division.
- Genomic location of HIV-1 integration in heterochromatin, centromeric regions, and low-expressed genes predisposes proviruses to latency.
- ZNF genes preferentially harbor latent proviruses due to their reduced expression and a heightened heterochromatinized chromatin state.

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PLAIN LANGUAGE SUMMARY

Where HIV inserts itself into a person's DNA helps determine whether the virus stays silent or becomes active. We found that the surrounding genetic environment plays a major role in allowing HIV to hide and persist, helping explain why curing HIV remains so challenging.